CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75633

CORRESPONDENCE

May 10, 2000

ORIG AMENDMENT

TARO

Office of Generic Drugs
Food and Drug Administration
Document Control Room
MPN II
7500 Standish Place, room 150
Rockville, Maryland
USA 20855-2773

Reference: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Telephone Amendment

Dear Sir:

Please find enclosed Taro Pharmaceuticals' Telephone Amendment for the above-referenced application.

As required by 21 CFR 314.96(d)(5), Taro is forwarding a copy of the technical data (including 356h form). Taro Pharmaceuticals Inc. certifies that the technical sections contained in this copy are true copies of the same sections submitted to OGD. If there are any questions relating to the information submitted, please contact us at:

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph. D.
V.P., Regulatory Affairs

Encl. : Field Copy

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May 10, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20857
USA

RE: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Telephone Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on May 7, 1999 pursuant to 21 CFR 314.70. and our Major Amendment of December 15, 1999. Reference is also made to the telephone conversation of May 10, 2000 between Elaine Hu, Paul Schwartz and Liang-Li Huang of the Agency and Lorraine Sachs of Taro Pharmaceuticals, during which the Agency requested that the page 4 of our Major Amendment (page 1110 of the original ANDA) be corrected to indicate the composition of the intended commercial batch kg).

In **supplementary page 1**, submitted is the revised page 4 of our Major Amendment (page 1110 of the original ANDA) indicating the qualitative/quantitative composition for the intended commercial size batch kg).

This completes our Telephone Amendment of May 10, 2000. If there are any questions with regards to this amendment, please do not hesitate to contact us at:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

April 18, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room, Metro Park North II
Att. Ms. Elaine Hu
7500 Standish Place, Room 150
Rockville MD 20857
USA

NEW CORRESP
NC

RE: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Major Amendment

Dear Madam,

As per you telephone request of today, please find attached the first page of our Major Amendment Letter of December 15, 1999, missing from the original Major Amendment. We apologize for any inconvenience this may have caused.

If you need any further information, please do not hesitate to contact us.

Sincerely,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
V.P. Regulatory Affairs

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December 15, 1999

Office of Generic Drugs
Food and Drug Administration
Document Control Room
MPN II
7500 Standish Place, room 150
Rockville, Maryland
USA 20855-2773

ORIG AMENDMENT
N/A C

ORIG AMENDMENT

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Reference: **ANDA 75-633**
Clobetasol Propionate Emollient Cream USP, 0.05%
Major Amendment

Dear Sir:

Please find enclosed Taro Pharmaceuticals' response to a recent deficiency letter from the FDA, dated November 22, 1999, for the above-referenced application.

As required by 21 CFR 314.96(d)(5), Taro is forwarding a copy of the technical data (including 356h form). Taro Pharmaceuticals Inc. certifies that the technical sections contained in this copy are true copies of the same sections submitted to OGD. If there are any questions relating to the information submitted, please contact our US Agent:

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph. D.
V.P., Regulatory Affairs

Encl. : Field Copy

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TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-4767
905-791-5008

2. **Please change the title of certificate of analysis for Dimethicone (350 cst) from to Dimethicone (350 cst) NF.**

Response

The specifications for Dimethicone (350 cst) have been revised to change the title from to Dimethicone (350 cst), NF, and are submitted in **supplementary page 30**.

3. **Please provide the batch record, release testing results, and available stability data of the scale-up batch, S114-51723, which was manufactured**

Response

The scale-up batch (L) S114-51723 was manufactured as an experimental scale-up batch in order to serve as a basis for the scale-up master manufacturing document as well as to be used in comparative in-vitro release testing with the biostudy batch. This batch was not packaged or put on stability, therefore no stability data on this batch are available.

Taro has manufactured another kg exhibit batch (L) S114-51806 using the proposed manufacturing procedure This batch was fully packaged, tested and monitored in both accelerated and room temperature stability study. The batch record, packaging work orders, release testing results and 3 months accelerated and room temperature stability data on the batch S114-51806 are provided in **supplementary pages 31 - 72**.

4. **The mixer attached to the mixing vessel two agitators, primary and secondary as described on page 1225. The agitator speed changed at different steps in the exhibit batch, S114-51531, but the batch record did not specify which agitator at each step. Please clarify.**

Response

Since primary and secondary agitators in the mixing vessel are attached to each other, the speed of one cannot be changed without changing the speed of the other. Therefore the agitator speed and the changes in the agitator speed in the batch record for the exhibit batch (L) S114-51531 were recorded as one numerical value, which represents the speed of the secondary agitator.

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

5. **on page 1398 is not acceptable. Please refer to the Guidance for Industry on Container Closure Systems. We recommend that you withdraw the protocol at this time.**

Response

Taro hereby withdraws the submitted on page 1398 of the original ANDA.

6. **Please revise the in-process control specification to establish the limit for**

Response

The limits for in-process specifications have been established as follows:

Separation:	NMT slight
Particulates (waxy lumps)/10 fields of view:	None
Crystals (µm):	None

Revised in-process/bulk product specifications are submitted in **supplementary page 73.**

7. **Please revise the in-process control, finished product, and stability specifications to establish the limits for viscosity.**

Response

The in-process, release and stability limits for viscosity have been established as follows:

Lower limit: NLT cps

Upper limit: Upper limits for in-process and release testing will be established based on the data obtained on the three process validation batches. Upper stability limits for viscosity will be set based on a minimum of 12 months RT stability data obtained on the process validation batches. CBE supplements proposing the above limits will be submitted to the Agency.

Revised in-process/bulk, packaged product and stability specifications are provided in **supplementary pages 73 - 75.**

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

8. **Please provide a sampling plan for the blend uniformity test in a production batch. We recommend the blend uniformity test acceptance criteria as % (mean of individual test results) with a maximum relative standard deviation (RSD) of %.**

Response

The in-process/bulk product specifications indicate that the sampling for the blend uniformity test will be performed from the beginning, middle and end of the bulk transfer from the mixing vessel to the holding container. The acceptance criteria for this test have been revised to be % LC (mean of individual test results). The allowable RSD has been set to NMT % due to the small number of samples (3).

In-process/bulk product specifications indicating the above changes are submitted in **supplementary page 73**.

9. **Please provide an antimicrobial preservative effectiveness test data at the 70% level of label claim of imidurea to justify the limits in the in-process, finished product, and stability specifications.**

Response

The Antimicrobial Preservative Efficacy Test Report for Clobetasol Propionate Emollient Cream, justifying the lower specification limit of % LC for Imidurea, is provided in **supplementary pages 76 - 77**.

10. **Please revise the finished product and stability specifications to establish limits for individual and total impurities.**

Response

Based on the stability data compiled to date, the following limits for degradation products have been established:

Degradation Products	Packaged Product Specifications	Stability Specifications
Individual	NMT %	NMT %
Total	NMT %	NMT %

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

The packaged product and stability specifications indicating the above limits are submitted in **supplementary pages 74 - 75**.

11. Please revise the stability protocol to commit that assay testing on accelerated stability samples will be performed from the top, middle, and bottom of the tube for all package sizes at all stability stations.

Response

Taro' Stability Protocol for Clobetasol Propionate Emollient Cream USP, 0.05%, submitted in **supplementary pages 78 - 79**, has been revised to indicate that the samples in both accelerated and room temperature stability testing will be tested from the top, middle and bottom of the tube for all package sizes at all stability time points.

12. Please revise the post-approval stability protocols to commit that expiration dates may be extended as three production batches, stability data, which justify the extension, are provided.

Response

The Postapproval Stability Commitment, presented in **supplementary page 80**, is now revised to state the following:

"As additional room temperature data, beyond 24 months, become available, the expiration date will be extended as warranted. The extension will be filed in annual reports in accordance with CFR 314.70 (d)(5), supported by the stability data obtained on three production size batches."

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. A satisfactory compliance evaluation of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

Response

We acknowledge that the facilities referenced in our ANDA relative to the drug substance and drug product manufacturing and testing must be in compliance with CGMP at the time of the application approval.

2. **Your analytical methodology is not identical to the US Pharmacopeial methods for the final drug product. Please be advised that the USP methods are the regulatory methods and will prevail in the event of any dispute.**

Response

We acknowledge that the USP methods are regulatory methods and will prevail in the event of any dispute.

3. **Please provide the up-to-date long term stability data for all package sizes.**

Response

Twelve months room temperature stability data for the exhibit batch (L) S114-51531 in all package sizes are provided in **supplementary pages 81 - 92.**

Bioequivalency Comments

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

Response

Acknowledged.

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

Labeling Deficiencies

1. GENERAL COMMENTS

a) The established name of this drug product is clobetasol propionate cream. The modifier "emollient" should appear separate from the established name (i.e. clobetasol propionate cream (emollient)).

b) Please note that USAN name are common nouns and should be treated as such in the text of labeling (i.e. lower case). Upper case may be used when the USAN name stands alone as on labels or the title of the package insert.

2. CONTAINER (15 g, 30 g, 45 and 60 g)

a) Change the "contains" statement to : Each gram contains: clobetasol propionate 0.5 mg in an ...

b) Include "Usual Dosage" before the "See package insert" statement.

3. CARTON (15 g, 30 g, 45 and 60 g)

a) See GENERAL COMMENTS

b) See CONTAINER comments.

4. INSERT

a) see GENERAL COMMENTS

b) DESCRIPTION

Change the molecular weight to "466.98" to be in accord with USP 23.

c) PRECAUTIONS (General)

Revise the 2nd sentence of the 7th paragraph to .....observing the failure....(including 'a")

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

d) ADVERSE REACTIONS

"Formulations in the first sentence of the first paragraph should be plural.

e) HOW SUPLLIED

Relocate "Rx only" to appear directly beneath the insert title.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference-listed drug. We suggest that you routinely monitor the following web site for any approval changes-

htpp://www.fda.gov/cder/ogd/rid/labeling_review_branch.htlm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Response

The labels and labeling have been revised as instructed above. The following has been provided:

Twelve (12) final printed labels:

- 15 g tube labels (**supplementary pages 93 - 104**)
- 15 g carton labels (**supplementary pages 105 - 116**)
- 30 g tube labels (**supplementary pages 117 - 128**)
- 30 g carton labels (**supplementary pages 129 - 140**)
- 45 g tube labels (**supplementary pages 141 - 152**)
- 45 g carton labels (**supplementary pages 153 - 164**)
- 60 g tube labels (**supplementary pages 165 - 176**)
- 60 g carton labels (**supplementary pages 177 - 188**)
- package insert (plastic pouch with the **supplementary page 189**)

Side-by-side comparison of the proposed labeling with the last submission with all differences annotated and explained is provided in **supplementary pages 190 - 205.**

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

This completes our response to the Agency's deficiency letter dated November 22, 1999. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

This Major Amendment is being submitted in two copies. In addition a third (Field copy) is enclosed.

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ V.Lucic
cc. Acting Director, FDA, Office of International Programs

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008

May 7, 1999

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Mr. Doug Sporn
Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA for Clobetasol Propionate Emollient Cream USP, 0.05 %**

Dear Mr. Sporn:

Taro Pharmaceuticals Inc. submits today an original Abbreviated New Drug Application (ANDA) seeking approval to market Clobetasol Propionate Emollient Cream USP, 0.05% that is bioequivalent to the listed drug, TEMOVATE E®, manufactured by Glaxo Wellcome Inc. pursuant to NDA 20-340.

This ANDA consists of four volumes. Taro Pharmaceuticals Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in orange folders. The diskette with the biostudy data is included in the archival copy, section VI "Bioavailability and Bioequivalence".

Taro Pharmaceuticals Inc. hereby certifies that, the field copy of this ANDA submission contained in burgundy folders is a true copy of the technical sections of the ANDA. The field copy also contains a copy of the signed 356h form and a certification that the contents are a true copy of the technical sections of the ANDA.

TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-4767
905-791-5008

If there are any questions regarding this application, or if additional information is required, please contact our US agent:

Taro Pharmaceuticals USA, Inc.,
Attn: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001

Sincerely,
Taro Pharmaceuticals Inc.

Derek Ganes, Ph.D.
V.P. , Regulatory Affairs

/Vesna Lucic

Enclosures:

Archival Copy (1 set):
All Sections (I - XX), 4 volumes (Blue)
Review Copies:
CMC (Sections I-V and VII-XX), 2 volumes (Red)
Bioequivalence (Sections I-VII): 3 volumes (Orange)
Field Copy (1 set)
CMC (Sections I-V and VII-XX), 2 volumes (Burgundy)

TARO PHARMACEUTICALS INC.
TELEPHONE
905-791-8276
1-800-268-1975
TELEFAX NO.
905-791-5008

March 8. 2000

TARO

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, MPN II
7500 Standish Place, Room 150
Rockville. MD 20855-2773

Re: ANDA #
ANDA #75-508 - Diflorasone Diacetate Cream, 0.05%
ANDA #75-633 - Clobetasol Propionate Emollient Cream, 0.05%
ANDA
ANDA #75-673 - Clotrimazole/Betamethasone Dipropionate Cream USP, 1%/0.05%

General Correspondence – Change in Ownership

Dear Sir/Madam:

Reference is made to our previous general correspondence dated December 21, 1999 concerning the change in ownership of the above referenced ANDA's, and to phone conversations with Ms. Nadine Warren of the Office of Generic Drugs on March 1 and March 8. 2000.

As requested by Ms.Warren, enclosed please find signed copies of form FDA 356h for each of these five ANDA's from the previous owner, Taro Pharmaceuticals Inc. in Bramalea. Ontario. Canada.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 www.taropharma.com